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# Impact of cumulative steroid dose on infectious diseases after allogenic hematopoietic stem cell transplantation

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## Conflict-of-interest disclosure

The authors declare no competing financial interests

## Abstract

Systemic steroid is used to treat various transplant-related complications after allogenic hematopoietic stem cell transplantation (allo-HSCT). However, measures to evaluate its impact on infections are still limited. Hence, we examined the cumulative steroid dose used within 30 days after transplant as a predictor of future risk of infections. This study included 226 patients who underwent their first allo-HSCT at Kyoto University Hospital between 2005 and 2015. Sixty-one patients received transplantation from related donors, 106 received unrelated BMT and 59 received unrelated single-unit CBT. Patients were categorized into 3 groups according to the cumulative steroid dose in terms of prednisolone: no-steroid group (n=174), low-dose group (<=7mg/kg) (n=22) and high-dose group (>7mg/kg) (n=30). In a multivariate analysis, high-dose steroid administration was associated with CMV antigenemia (HR 1.91, P=0.037) and bacteremia (HR 2.59, P=0.053). No impact was found on the occurrence of invasive fungal infection. In conclusion, high-dose cumulative steroid could predict high risks of bacteremia and CMV antigenemia. Additional anti-bacterial agents for fever and regular measurement of CMV antigen are recommended for whom with systemic steroid administration even after neutrophil engraftment.

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## Introduction

Systemic steroid is frequently used as a primary treatment for transplant-related complications such as graft-versus-host disease (GVHD) and non-infectious pulmonary complications after allogeneic hematopoietic stem cell transplantation (HSCT)[1–3]. The use of systemic steroid along with the occurrence of GVHD has been suggested to be a risk factor for various infectious diseases[4–8], which are main causes of transplant-related mortality. Since the number of HSCTs with a higher risk of complications, such as cord blood transplantations (CBT) and HLA mismatch transplantations in older patients, has been increasing[9–12], it is important to evaluate the effect of steroid use on clinical outcomes.

The associations between the cumulative dose of steroid and the occurrence of side effects have been discussed in patients with non-hematologic diseases who receive systemic steroid for a prolonged period. The impact of the cumulative dose of steroid on infectious complications has been controversial, although a positive association was noted in patients taking immunosuppressive agents after solid organ transplantations[13–16]. Similarly, in recipients of HSCT, steroid administration could increase the risk of infectious complications because of the concomitant use of calcineurin inhibitors and the delay of immune reconstitution after HSCT. However, there is little information available regarding the steroid dose. Hence, in the present study, we examined the impact of the cumulative steroid dose on the risk of infectious diseases after HSCT in a single transplant center.

# Methods

## Data collection

A total of 238 patients who underwent their first allogeneic HSCT for hematologic diseases at Kyoto University Hospital from 2005 to 2015 and survived at least 30 days after transplantation were included. Patients who had already started to receive steroid before transplantation were excluded. Patients who had active bacterial, fungal, or viral infection at transplantation or who had had history of invasive fungal infection before transplantation were also excluded. The Institutional Review Board of Kyoto University Hospital, where this study was organized, approved this study.

## Treatment Policy and Definition

*Definitions*

Neutrophil engraftment was diagnosed when an absolute neutrophil count over 500/μL was observed for 3 days in a row. Acute GVHD was diagnosed and classified by each physician according to traditional criteria[17].

*Invasive fungal infections*

βD-glucan was examined once a week, and imaging inspection and blood culture were examined for fever or other suspicious conditions. Diagnoses of invasive fungal infections were categorized into 3 types; possible, probable, and proven, based on the practice guidelines from the Infectious Diseases Society of America (IDSA) and Japanese guidelines[18–20].

In our hospital, antifungal prophylaxis was administered in all patients who underwent allo-HSCT. The antifungal agents that were generally used as prophylaxis were oral fluconazole, voriconazole, micafungin and liposomal

amphotericin B injection, according to each patient's history of fungal infection.
All patients were hospitalized in a cleanroom of ISO Class 5 (ISO 14644-1)[21] before and in the early period after day0 and moved to a cleanroom of ISO Class 6 (ISO 14644-1)[21] after they achieved neutrophil engraftment.

*CMV antigenemia and CMV disease*

CMVpp65 antigen examinations were performed using C10/11[22] method or C7-HRP[23] method once a week for every patient after transplantation and examined additionally for suspicious symptoms of CMV diseases.
In cases with more than 3 positive cells in 2 slides (C10/C11 method) or more than 2 positive cells out of 50000 WBC (C7-HRP method), pre-emptive therapy was given followed by close CMV-antigen monitoring[22,23]. Diagnosis of CMV end-organ diseases were diagnosed according to published definitions[24].

*Other viremias*

Patients were examined by viral PCR detection at the timing of fever of unknown origin or any other symptoms of infection based on the judgment of each physician in charge. Viruses examined in PCR included adenovirus, BK virus, JC virus, varicella zoster virus, human herpes simplex, EB virus and other viruses according to each patient's symptoms.

*Bacteremia*

Two sets of blood culture were examined for each patient with fever or any other symptoms suggesting infectious diseases. As our policy, antibacterial prophylaxis was not applied in every patient, except for those who were at high risk of bacterial infection, such as those with a history of repeated severe

bacterial infection or a long history of chemotherapeutic treatment.

**Endpoints**

The endpoint of this study was the incidence of various infectious diseases including invasive fungal infection, cytomegalovirus (CMV) antigenemia, and bacteremia diagnosed from 30 days to 6 months after HSCT. The cumulative steroid dose was calculated as the total amount administered per patient within 30 days after transplantation, since the first steroid administration mainly began within this period as a treatment for pre-engraftment or engraftment syndrome and for acute GVHD.

**Statistical analysis**

Descriptive statistics were used to summarize variables related to patient characteristics. We calculated the cumulative steroid dose within 30 days after HSCT. The landmark day was set at 30 days after transplantation. Prednisolone-equivalent conversion was performed in accordance to the general formula[25]. Episodes of infectious diseases (invasive fungal infection, CMV antigenemia or disease, and bacteremia) were calculated based on cumulative incidence curves. A competing event was death without infectious disease. Cumulative incidences in the groups were compared using the Gray test. Fine and Gray's proportional hazards model was used to evaluate the effect of cumulative steroid dose on the occurrence of infectious diseases[26]. The following covariates were considered; recipient's sex, age (<50 or ≥50 years old), disease diagnosis (myeloid malignancies, lymphoid malignancies, or others), year of transplantation (2005-2009 or 2010-2016), disease status (complete remission [CR] or non-CR), donor type (bone marrow transplantation

from unrelated donor, peripheral blood stem cell transplantation from related donor, or CBT), conditioning regimen (reduced-intensity or myeloablative), GVHD prophylaxis (tacrolimus or cyclosporine in addition to mycophenolate mofetil or methotrexate), presence or absence of neutrophil engraftment at day 30, and prophylactic administration of levofloxacin. All factors, in addition to the main effect, were selected with a variable retention criterion of $P<0.05$ in the univariate analysis and analyzed in the multivariate analysis.

Although acute GVHD has been suggested to be a risk factor for infectious diseases after HSCT, we did not include acute GVHD because there was a correlation between acute GVHD and steroid administration (data not shown), and it would be inappropriate to include both in the same model.

All statistical analyses were performed with Stata version 14 (Stata Corp, College Station, TX) and EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, version 3.1.1, Vienna, Austria).

# Results

## Patient characteristics

Sixty-one patients received transplantation from a related donor, 106 received unrelated bone marrow grafts, and 59 received unrelated cord blood units. Their median age was 51 years (range, 17–66). Neutrophil engraftment was achieved in 203 patients (90%) by day 30 and mean neutrophil engraftment day from transplantation in each graft were 21 in bone marrow transplantation, 17 in peripheral blood stem cell transplantation and 25 in cord blood transplantation. Patients were categorized into 3 groups according to the cumulative steroid dose within 30 days: no steroid group (n = 174), low-dose cumulative steroid group (7mg/kg or less of prednisolone-equivalent dose, n = 22), and high-dose cumulative steroid group (over 7mg/kg of prednisolone-equivalent dose, n =30). The cutoff value of 7mg/kg of prednisolone-equivalent dose approximately stands for initial steroid treatment against acute GVHD in Japan (1mg/kg during 7 days at maximum). The reason for steroid administration was treatment for GVHD in 33 patients, engraftment syndrome in 9, and other reasons including lung complications in 10. Grade II to IV acute GVHD was diagnosed in 96 patients in total. There was no obvious difference in background among the different donor sources. (Table 1).

## Invasive fungal infection

We observed 13 cases of invasive fungal infection, including one proven case with candida bloodstream infection and 2 probable and 10 possible cases of pneumonia. The cumulative incidence of invasive fungal infection at 6 months was 5.7%, 4.5%, and 6.7% in the no-administration, low-dose, and high-dose groups, respectively (P = 0.231, Gray test) (Figure 1). Multivariate analysis

showed no association between steroid administration and the occurrence of invasive fungal infection. We found no other significant risk factor.

**CMV antigenemia and diseases**

Eighty-six HSCT were performed from CMV-antibody (Ab) positive donors to CMV-Ab positive recipients, 10 were from CMV-Ab positive donors to CMV negative recipients and the other 103 were from CMV-Ab negative donors (Table 1).

A total of 105 (46%) patients were diagnosed as CMV antigenemia and 81 (78%) received Ganciclovir as a pre-emptive antiviral therapy. Seven patients were pathologically diagnosed as CMV disease including colitis and hepatitis, all of whom were positive for CMV antigenemia. There were 4 cases of CMV antigenemia with clinically suspected CMV diseases, although they were not definitely diagnosed due to a lack of pathological evidence. No patient died of CMV-related complications. The cumulative incidences of CMV antigenemia at 6 months in the no-administration, low-dose, and high-dose groups were 49.7%, 68.8%, and 69.6%, respectively (P = 0.038) (Figure 2). Reason for steroid initiation had little impact on the occurrence of CMV antigenemia (GVHD vs other reasons: HR 2.119, P=0.089). Multivariate analysis showed that both a low-dose and high-dose of cumulative steroid administration were associated with CMV reactivation, although the association in the low-dose group was not statistically significant (low-dose vs. no-administration group: HR 1.64, P=0.100, high-dose vs. no-administration group: HR 1.91 P = 0.037). Other risk factors detected were cord blood unit as a donor source (cord blood unit vs. sibling donor: HR 1.62, P = 0.018) and recipient age over 50 years at transplantation (age >=50 vs. <50: HR 1.62, P = 0.007) (Table 2).

## Viral infections other than CMV

A total of 15 cases were diagnosed as viremia including Adenovirus in 1 patient, BK virus in 2, Epstein Barr virus in 1, Varicella Zoster virus in 3, and human herpes virus 6 in 7. Ten patients were in the no-administration group and there was no association between viremia and the cumulative steroid dose.

## Bacteremia

The cumulative incidences of bacteremia at 6 months in the no-administration, low-dose, and high-dose groups were 9.3%,15.8%, and 21.7%, respectively (P = 0.224) (Figure 3). Detected microbes at the first onset of bacteremia were gram-negative rods in 15 cases, gram-positive cocci in 7 cases, and gram-positive rods in 1 case. Reason for steroid initiation had little impact on the occurrence of bacteremia (GVHD vs other reasons: HR 4.89, P=0.14). Administration of levofloxacin showed no apparent prophylactic effect on bacteremia (HR 0.73, P=0.574).

Multivariate analysis showed that the high-dose group was marginally associated with an increased risk of bacteremia (low-dose vs. no-administration group: HR 2.13, P =0.240, high-dose vs. no-administration group: HR 2.59, P = 0.053). Regarding the microbes detected, there was no significant difference among the three groups. The other major risk factor for bacteremia was a recipient age over 50 years at transplantation, which had a HR of 2.69 (age >=50 vs. <50: P = 0.021) (Table 3).

## Other bacterial infections

The other infectious events proven as bacterial complications were 4 cases

*Clostridium difficile* colitis, 2 cases of pneumonia (1 of *Pseudomonas aeruginosa*, 1 of *Stenotrophomonas maltophilia*), 1 cellulitis of *Coagulase-negative staphylococcus*, and 1 endophthalmitis of *Coagulase-negative staphylococcus*.

## Discussion

In the present study, we examined the impact of the cumulative dose of steroid on infectious complications after HSCT and found associations between steroid dose and both CMV and bacterial infections following HSCT.

Although acute GVHD and systemic steroid have been reported to be risk factors for invasive fungal infection after HSCT[27–30], the cumulative steroid dose was not associated with fungal infection in our study. All patients in our hospital continued prophylactic treatment with antifungal drugs according to the risk of fungal infection, following Japanese and European guidelines[31]. Only 13 of 226 patients had invasive fungal infection over 10 years, although our cohort included a relatively large number of cord blood transplantations. This suggests that fungal infection could be avoided regardless of the occurrence of acute GVHD, steroid use, and donor source by appropriate clinical practice.

With regard to CMV-related complications, steroid use was strongly associated with CMV antigenemia regardless of the cumulative dose, which is similar to previous reports[4,32,33]. Almost all the patients in our cohort were seropositive before transplant and thus CMV antigen levels must be measured regularly after HSCT. Another risk factor for CMV antigenemia was cord blood unit as a donor source, although the HR was lower than previously reported and there were no CMV-related deaths. Older patients also had a higher risk of CMV antigenemia. Contrary to a previous report[4], myeloablative conditioning was not found to be a risk factor for CMV antigenemia, which is probably due to the difference in the conditioning regimen or the medication used for GVHD prophylaxis.

High-dose, but not low-dose, cumulative steroid administration was a risk factor for bacterial infection. Anti-bacterial prophylaxis and preemptive therapies for fever of undetected origin might be better considered for patients after HSCT receiving a high cumulative dose of steroid, regardless of their neutrophil count. An advanced age at transplant was another risk factor for bacterial infection after HSCT, which was consistent with previous reports[34].

The present study has several limitations. First, this is a retrospective study of small population with heterogeneous background in a single transplant center. Second, the loads of viruses other than CMV were not regularly measured and the timing of the examination was determined by each physician in charge. Finally, information on blood sugar levels was not collected, although blood sugar levels were checked regularly and treated by continuous intravenous insulin infusion, which minimized the effect of hyperglycemia on bacterial infections.

In conclusion, our study confirmed that the cumulative steroid dose could be a good prognostic marker for CMV antigenemia and bacterial infection after HSCT. These post-transplant complications must be detected and managed in the early period, particularly in elderly patients who are receiving a high cumulative dose of steroid.

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# Figure legends

## Figure 1 Cumulative incidence of invasive fungal infection

## Figure 2 Cumulative incidence of CMV antigenemia

## Figure 3 Cumulative incidence of bacteremia

**Table1 Patient characteristics**

| Group by cumulative steroid dose within 30 days | | Total | No administration (n=174) value | | Low (<=7mg/kg PSL) (n=22) value | | High (>7mg/kg PSL) (n=30) value | | Variance |
|---|---|---|---|---|---|---|---|---|---|
| | | n[*1] | n | %[*2] | n | % | n | % | P-Value |
| Age[*3] median(range) | | | 51 (17-66) | | 47 (21-66) | | 48 (20-66) | | 0.651 |
| Gender | Male | 126 | 103 | 59.2 | 9 | 40.9 | 14 | 46.7 | 0.144 |
| | Female | 100 | 71 | 40.8 | 13 | 59.1 | 16 | 53.3 | |
| Donor source | Sibling | 61 | 47 | 27.0 | 7 | 31.8 | 7 | 23.3 | 0.930 |
| | Unrelated BM | 106 | 81 | 46.6 | 9 | 40.9 | 16 | 53.3 | |
| | Unrelated CB | 59 | 46 | 26.4 | 6 | 27.3 | 7 | 23.3 | |
| Disease | AML/MDS | 134 | 113 | 64.9 | 11 | 50.0 | 10 | 33.3 | 0.015 |
| | ALL/other leukemias | 50 | 30 | 17.2 | 8 | 36.4 | 12 | 40.0 | |
| | Malignant lymphoma | 35 | 25 | 14.4 | 3 | 13.6 | 7 | 23.3 | |
| | Aplastic anemia | 7 | 6 | 3.4 | 0 | 0.0 | 1 | 3.3 | |
| Disease status | CR | 94 | 72 | 41.4 | 11 | 50.0 | 11 | 36.7 | 0.652 |
| | non CR | 132 | 102 | 58.6 | 11 | 50.0 | 19 | 63.3 | |
| Conditioning intensity | Myeloablative | 112 | 86 | 49.4 | 11 | 50.0 | 15 | 50.0 | 1.000 |
| | Reduced intensity | 114 | 88 | 50.6 | 11 | 50.0 | 15 | 50.0 | |
| Neutrophil engraftment at Day30 | No | 20 | 18 | 10.5 | 1 | 4.5 | 1 | 3.4 | 0.477 |
| | Yes | 203 | 154 | 89.5 | 21 | 95.5 | 28 | 96.6 | |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| levofloxacin prophylaxis | NO | 181 | 142 | 84.0 | 14 | 63.6 | 25 | 89.3 | 0.079 |
| | Yes | 38 | 27 | 16.0 | 8 | 36.4 | 3 | 10.7 | |
| GVHD prophylaxis | CI | 19 | 12 | 6.9 | 2 | 9.1 | 5 | 16.7 | 0.755 |
| | CI+MMF | 35 | 27 | 15.5 | 4 | 18.2 | 4 | 13.3 | |
| | CI+MTX | 137 | 107 | 61.5 | 13 | 59.1 | 17 | 56.7 | |
| | CI+MMF+MTX | 35 | 28 | 16.1 | 3 | 13.6 | 4 | 13.3 | |
| GVHD grade at onset | I | 38 | 30 | 34.5 | 6 | 30.0 | 2 | 7.4 | 0.092 |
| | II | 76 | 47 | 54.0 | 11 | 55.0 | 18 | 66.7 | |
| | III | 14 | 6 | 6.9 | 2 | 10.0 | 6 | 22.2 | |
| | IV | 6 | 4 | 4.6 | 1 | 5.0 | 1 | 3.7 | |
| CMV resopositivity | Donor+/ Recipient+ | 86 | 63 | 41.2 | 9 | 45.0 | 14 | 53.8 | 0.527 |
| | Donor+/ Recipient- | 10 | 9 | 5.9 | 0 | 0.0 | 1 | 3.8 | |
| | Donor-/ Recipient+ | 85 | 64 | 41.8 | 10 | 50.0 | 11 | 42.3 | |
| | Donor-/ Recipient- | 18 | 17 | 11.1 | 1 | 5.0 | 0 | 0.0 | |
| Reason for steroid | Acute GVHD | 32 | | | 13 | 59.1 | 19 | 63.3 | |
| | Engraftment syndrome | 9 | | | 3 | 13.6 | 6 | 20.0 | |
| | Others | 11 | | | 6 | 27.3 | 5 | 16.7 | |

*1n indicates the number of patients with each characteristics

*2% indicates the percentage of patients in each steroid group

*3Age indicates patients' age at transplantation

Calcinerin inhibitors include Tacrolimus and Cyclosporin

Abbreviation: AML, acute myeloid leukemia; MDS, myelodysplastic syndrome; ALL, acute lymphoblastic leukemia; CR, complete remission; BM, bone marrow; CB, cord blood; GVHD, graft-versus-host disease; CI, Calcinerin inhibitor; MMF, mycophenolate mofetil; MTX, methotrexate; PSL, prednisolone

**Table 2 Univariate and multivariate analysis of CMV antigenemia**

| Variables | | Univariate analysis | | | Multivariate analysis | | |
|---|---|---|---|---|---|---|---|
| | | HR | 95% CI | P-Value | HR | 95% CI | P-Value |
| Age*1 | <50 | 1.00 | | reference | 1.00 | | reference |
| | ≧50 | 1.46 | (1.01-2.09) | 0.042 | 1.62 | (1.14-2.30) | 0.007 |
| Gender | Male | 1.00 | | reference | | | |
| | Female | 0.88 | (0.60-1.28) | 0.499 | | | |
| Year of trasnplant | 2005-2009 | 1.00 | | reference | | | |
| | 2010-2015 | 1.19 | (0.81-1.74) | 0.373 | | | |
| Donor source | Sibling | 1.00 | | reference | 1.00 | | reference |
| | Unrelated BM | 1.10 | (0.68-1.78) | 0.687 | | | |
| | Unrelated CB | 1.64 | (1.00-2.68) | 0.047 | 1.62 | (1.09-2.40) | 0.018 |
| Disease | AML/MDS | 1.00 | | reference | | | |
| | ALL/other leukemias | 1.43 | (0.88-2.31) | 0.140 | | | |
| | Malignant lymphoma | 0.93 | (0.50-1.75) | 0.824 | | | |
| | Aplastic anemia | 1.46 | (0.54-3.93) | 0.453 | | | |
| Disease status | CR | 1.00 | | reference | | | |
| | non CR | 1.18 | (0.80-1.75) | 0.394 | | | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Conditioning regimen | Myeloablative | 1.00 | | reference | | | |
| | Reduced intensity | 1.19 | (0.81-1.74) | 0.369 | | | |
| GVHD prophylaxis | CI | 1.00 | | reference | | | |
| | CI+MMF | 1.00 | (0.50-1.99) | 0.994 | | | |
| | CI+MTX | 0.65 | (0.35-1.21) | 0.178 | | | |
| | CI+MMF+MTX | 1.10 | (0.54-2.22) | 0.792 | | | |
| Neutrophil engraftment at day30 | NO | 1.00 | | | | | |
| | Yes | 1.46 | (0-86-2.50) | 0.164 | | | |
| steroid group | No administration | 1.00 | | reference | 1.00 | | reference |
| | Low-dose*2 | 1.58 | (0.87-2.87) | 0.140 | 1.64 | (0.91-2.96) | 0.100 |
| | High-dose*3 | 1.78 | (1.02-3.12) | 0.044 | 1.91 | (1.04-3.50) | 0.037 |

*1Age indicates patients' age at transplantation

*2Low-dose indicates group who undertook low cumulative dose of steroid (<=7mg/kg of prednisolone)

*3High-dose indicates group who undertook high cumulative dose of steroid (>7mg/kg of prednisolone)

Calcinerin inhibitors include Tacrolimus and Cyclosporin

Abbreviation: HR, hazard ratio; AML, acute myeloid leukemia; MDS, myelodysplastic syndrome; ALL, acute lymphoblastic leukemia; CR, complete remission; BM, bone marow; CB, cord blood; GVHD, graft-versus-host disease; CI, Calcinerin inhibitor; MMF, mycophenolate mofetil; MTX, methotrexate; PSL, prednisolone

**Table 3 Univariate and multivariate analysis of bacteremia**

| Variables | | Univariate analysis | | | Multivariate analysis | | |
|---|---|---|---|---|---|---|---|
| | | HR | 95% CI | P-Value | HR | 95% CI | P-Value |
| Age*1 | <50 | 1.00 | | reference | 1.00 | | reference |
| | ≧50 | 2.40 | (1.07-5.38) | 0.034 | 2.69 | (1.16-6.22) | 0.021 |
| Gender | Male | 1.00 | | reference | | | |
| | Female | 1.20 | (0.52-2.78) | 0.671 | | | |
| Year of trasnplant | 2005-2009 | 1.00 | | reference | | | |
| | 2010-2015 | 1.11 | (0.48-2.53) | 0.813 | | | |
| Donor source | Sibling | 1.00 | | reference | | | |
| | Unrelated BM | 1.28 | (0.46-3.55) | 0.633 | | | |
| | Unrelated CB | 1.18 | (0.37-3.72) | 0.778 | | | |
| Disease | AML/MDS | 1.00 | | reference | | | |
| | ALL/other leukemias | 1.06 | (0.36-2.77) | 0.917 | | | |
| | Malignant lymphoma | 1.52 | (0.52-3.96) | 0.419 | | | |
| | Aplastic anemia | | | | | | |
| Disease status | CR | 1.00 | | reference | | | |
| | non CR | 1.63 | (0.66-3.98) | 0.287 | | | |
| Conditioning regimen | Myeloablative | 1.00 | | reference | | | |
| | Reduced intensity | 1.70 | (0.72-4.03) | 0.226 | | | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| GVHD prophylaxis | CI | 1.00 | | reference | | | |
| | CI+MMF | 1.61 | (0.31-9.13) | 0.568 | | | |
| | CI+MTX | 0.72 | (0.15-3.37) | 0.674 | | | |
| | CI+MMF+MTX | 1.16 | (0.24-6.58) | 0.864 | | | |
| Neutrophil engraftment at day30 | NO | 1.00 | | | | | |
| | Yes | 3.86 | (0.23-64.05) | 0.346 | | | |
| Levofloxacin prophylaxis | NO | 1.00 | | | | | |
| | Yes | 0.73 | (0.250-2.159) | 0.574 | | | |
| steroid group | No administration | 1.00 | | reference | 1.00 | | reference |
| | Low-dose*2 | 1.74 | (0.50-6.07) | 0.390 | 2.13 | (0.60-7.51) | 0.240 |
| | High-dose*3 | 2.27 | (0.87-5.93) | 0.097 | 2.59 | (0.99-6.78) | 0.053 |

*1Age indicates patients' age at transplantation

*2Low-dose indicates group who undertook low cumulative dose of steroid (<=7mg/kg of prednisolone)

*3High-dose indicates group who undertook high cumulative dose of steroid (>7mg/kg of prednisolone)

Calcinerin inhibitors include Tacrolimus and Cyclosporin

Abbreviation: HR, hazard ratio; AML, acute myeloid leukemia; MDS, myelodysplastic syndrome; ALL, acute lymphoblastic leukemia; CR, complete remission; BM, bone marow; CB, cord blood; GVHD, graft-versus-host disease; CI, Calcinerin inhibitor; MMF, mycophenolate mofetil; MTX, methotrexate; PSL, prednisolone

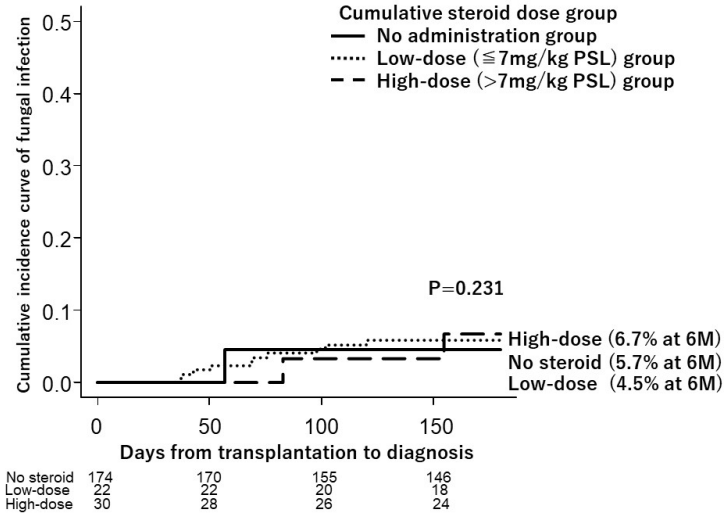


**Figure 1. Cumulative incidence of invasive fungal infection**

Figure 1

338x190mm (96 x 96 DPI)

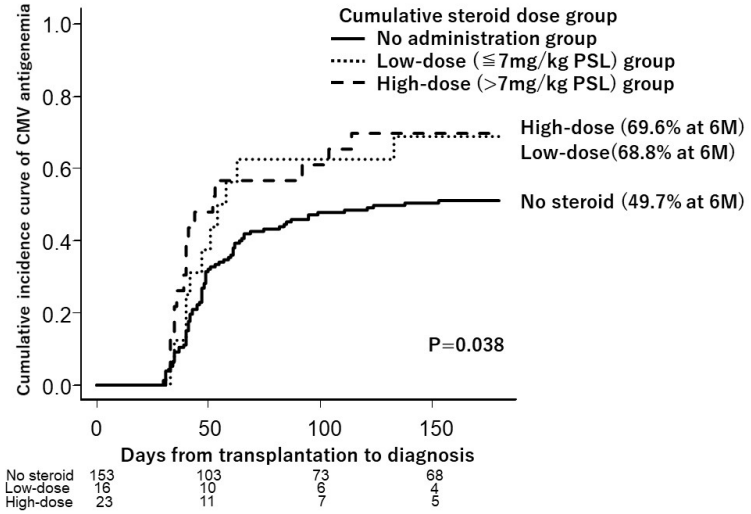


**Figure 2. Cumulative incidence of CMV antigenemia**

Figure 2

338x190mm (96 x 96 DPI)

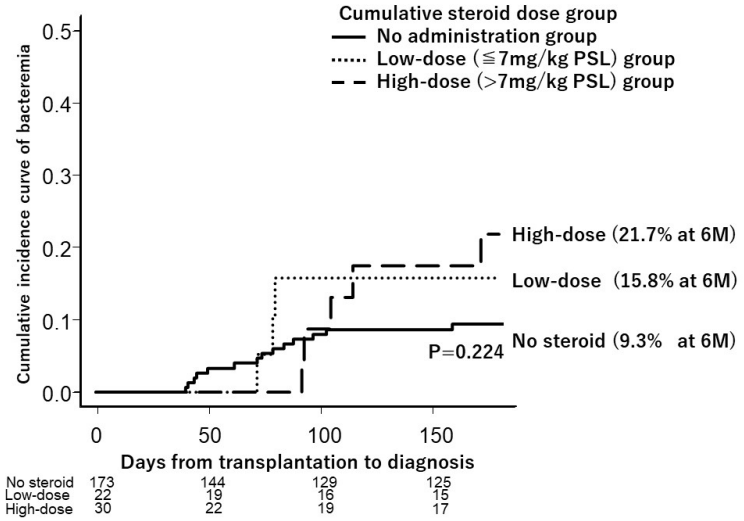


**Figure 3. Cumulative incidence of bacteremia**

Figure 3

338x190mm (96 x 96 DPI)